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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/749,119	12/30/2003	Richard L. Boyd	286336.152US1/NOR-013CP2	3286
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WILMERHALE/BOSTON 60 STATE STREET BOSTON, MA 02109			EXAMINER LI, QIAN JANICE	
			ART UNIT	PAPER NUMBER
			1633	
			NOTIFICATION DATE	DELIVERY MODE
			11/01/2007	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary

Application No.

10/749,119

Applicant(s)

BOYD, RICHARD L.

Examiner

Q. Janice Li, M.D.

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 31 August 2007.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 19-26, 28-40, 42-44, 46-49, 53 and 55-75 is/are pending in the application.
- 4a) Of the above claim(s) 21, 22, 24, 26, 32, 33, 37, 44, 53, 56, 61, 63, 67, 71-75 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 19, 20, 23, 25, 28-31, 34-36, 38-40, 42, 43, 46-49, 55, 57-60, 62, 64-66 and 68-70 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☒ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 30 December 2003 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☒ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. _____.
 - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date _____
- 4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____
- 5) ☐ Notice of Informal Patent Application
- 6) ☐ Other: _____

DETAILED ACTION

Election/Restrictions

Applicant's election with traverse of Group I, is acknowledged. The elected invention is drawn to a method of inducing graft tolerance in a patient, and species election drawn to a combination of the following: depleting T cells with chemotherapy before thymus reactivation in a post-puberty patient, reactivate thymus with leuprolide, and administering hematopoietic cells to inducing tolerance to an allogenic organ/tissue. Upon further consideration, group IV, (claims 69, 70) has been rejoined with group I, and the restriction between groups IV and I is hereby withdrawn. Claims 19, 20, 23, 25, 28-31, 34-36, 38-40, 42, 43, 46-49, 55, 57-60, 62, 64-66, 68-70 read on the elected invention.

The traversal is on the ground(s) that if members of a Markush group are sufficiently few in number the examiner must examine all the members of the group. In response, the claims are not drawn to a simple Markush group. The claims embrace various combinations of many elements, each element may be selected from a Markush group, and hence, the various combinations would encompass multitude of species. Thus it is maintained that each of the Inventions requires a separate search status and consideration. The inventions are mutually exclusive and independent methods for inducing tolerance using different materials (means of T cell depletion, means of thymus reactivation, HSCs, or dendritic cells, etc.), and method steps. The different materials belong to different chemical entities and have distinct mode of operation, require

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different search criteria and technical consideration. As such, the Invention and species requires different reagents, steps, protocols, and other considerations. The searches for different groups and species would have certain overlap, but they are not co-extensive. M.P.E.P. states, "FOR PURPOSES OF THE INITIAL REQUIREMENT, A SERIOUS BURDEN ON THE EXAMINER MAY BE PRIMA FACIE SHOWN IF THE EXAMINER SHOWS BY APPROPRIATE EXPLANATION OF SEPARATE CLASSIFICATION, OR SEPARATE STATUS IN THE ART, OR A DIFFERENT FIELD OF SEARCH AS DEFINED IN MPEP § 808.02". Therefore, it is maintained that these inventions are distinct due to their divergent subject matter. Further search of these inventions is not co-extensive, as indicated by the separate classifications. The requirement is still deemed proper and is therefore made **FINAL**.

Please note that after a final requirement for restriction, the Applicants, in addition to making any response due on the remainder of the action, may petition the Commissioner to review the requirement. Petition may be deferred until after final action on or allowance of claims to the invention elected, but must be filed not later than appeal. A petition will not be considered if reconsideration of the requirement was not requested. (See § 1.181.).

Claims 19-26, 28-40, 42-44, 46-49, 53, 55-75 are pending, however, claims 21, 22, 24, 26, 32, 33, 37, 44, 53, 56, 61, 63, 67, 71-75 are withdrawn from further consideration by the Examiner, pursuant to 37 CFR 1.142(b), as being drawn to non-elected inventions, there being no allowable generic or linking claim. Claims 19, 20, 23, 25, 28-31, 34-36, 38-40, 42, 43, 46-49, 55, 57-60, 62, 64-66, 68-70 are under current examination.

Specification

The first section of the specification refers to multiple applications in the continuation chain. The status of each application should be updated.

Claim Objections

Claim 35 is objected to because of the following informalities: LHRH should be spelled-out the first time it appears in the claim. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 19, 20, 23, 25, 28-31, 34-36, 38-40, 42, 43, 46-49, 55, 57-60, 62, 64-66, 68-70 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The claims are vague and indefinite because of the claim recitation, "a *mismatched* donor". The specification fails to define the term "mismatch", it is uncertain, in what aspect the donor and recipient mismatches, and thus the metes and bounds of the claims are unclear.

Claims 36, 71 contain trademark/trade names. Where a trademark or trade name is used in a claim as a limitation to identify or describe a particular material or

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product, the claim does not comply with the requirements of 35 U.S.C. 112, second paragraph. See *Ex parte Simpson*, 218 USPQ 1020 (Bd. App. 1982). The claim scope is uncertain since the trademark or trade name cannot be used properly to identify any particular material or product. A trademark or trade name is used to identify a source of goods, and not the goods themselves. Thus, a trademark or trade name does not identify or describe the goods associated with the trademark or trade name. In the present case, the trademark/trade name is used to identify/describe LHRH agonists and, accordingly, the identification/description is indefinite.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 19, 20, 23, 25, 28-31, 34-36, 38-40, 42, 43, 46-49, 55, 57-60, 62, 64-66, 68-70 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for inducing tolerance in a patient to a MHC-mismatched graft by immune suppression and administration of hematopoietic or mesenchymal stem cells, does not reasonably provide enablement for inducing graft-tolerance by reactivating thymus. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The factors to be considered when determining whether the disclosure satisfies the enablement requirements and whether undue experimentation would be required to make and use the claimed invention are summarized in *In re Wands*, (858 F2d 731, 737, 8 USPQ 2d 1400, 1404, (Fed Cir.1988)). These factors include but are not limited to the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability of the art, the breadth of the claims, and amount of direction provided. The factors most relevant to this rejection are the scope of the claims relative to the state of the art and the levels of the skilled in the art, and whether sufficient amount of direction or guidance are provided in the specification to enable one of skill in the art to practice the claimed invention.

The invention is directed to inducing tolerance to a graft from a mismatched donor via the steps of a) T cell depletion/immune suppression, b) reactivation of thymus of the recipient, and c) administering stem cells.

It is also noted that the claimed process contains at least two steps known to induce immune tolerance, i.e. a) depletion of T cells or immune suppression, and c) administration of stem and progenitor cells. Immune suppression or T cell depletion is the routine preparation for bone marrow transplantation to prevent immune rejection. The knowledge of administering stem cells for inducing tolerance could be seen in the teaching of *Sykes et al* (US 2002/0159999) and *McIntosh et al* (USP 6,368,636). *Sykes et al* teach peripheral stem cell (CD34+ HSCs) administration promote engraftment, mixed chimerism, and preferably long-term deletional tolerance in graft recipients (see e.g. the abstract and paragraph 0079). *McIntosh et al* (USP 6368636) teach

administration of bone marrow MSCs can reduce or prevent graft rejection. Thus, when a process includes multiple means of inducing tolerance, it is unclear whether the induced tolerance is caused by the known steps or by reactivation of thymus. To this end, the specification fails to provide any evidence that any graft tolerance was induced by the reactivation of thymus, but not by the well known means in the art. The specification only prophetically teaches (paragraph 0245) in the context of the skin graft *"The results will show that donor Balb/cJ skin transplanted onto a donor-reconstituted C57BL/6J mouse who has been castrated 'takes' (i.e., is accepted) better than the donor skin transplanted onto a donor-reconstituted C57BU6J mouse who is sham-castrated"* (emphasis added). In view of such, the specification fails to provide sufficient support for what is now claimed.

The specific teaching is necessary because it was still controversial in the art concerning the correlation between thymus reactivation and graft rejection. In fact, the art of record is replete with the evidence contrary to what is now claimed. For example, *Takami et al* (J Heart Lung Transplant 1995;14:529-36) teach orchiectomy (activating thymus through castration) had no influence on graft survival time or grade of rejection (e.g. the abstract). *Schofield et al* (J Heart Lung Transplant 2002;21:493-5) reported that the leuprolide hormone therapy appears to increase the risk of cardiac allograft rejection. *Antus et al* (Transpl Int 2002;15:494-501) teach testosterone treatment increases graft rejection while estrogens reduced the degree of graft rejection. It is particularly noteworthy that *Sykes et al* (US 2002/0159999) teach in the context of inducing graft tolerance the steps of immune suppression or T cell depletion, and

administration of hematopoietic stem cells, while thymus is deactivated by radiation to "make space" for the stem cell transplantation. This step directly contradicts what is now claimed. Accordingly, in view of the state of the art, it is particularly important that the applicant provides specific support for what is now claimed. To this end, the specification only prophetically teaches that the claimed invention would induce tolerance, and fails to shed light on the state of the art, and thus fails to provide an enabling disclosure for what is now claimed.

Therefore, in view of the limited guidance, the lack of predictability of the art and the breadth of the claims, one skill in the art could not practice the invention without undue experimentation as it is broadly claimed.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless —

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 19, 20, 23, 25, 28-31, 34-36, 42, 43, 46, 55, 57-59, 62, 64-66, 68-70 are rejected under 35 U.S.C. 102(b) as being anticipated by *Ghalie et al* (Am J Hematol 1993;42:350-3).

Ghalie et al teach a method comprising ablating the patient's T cells by total body irradiation and cyclophosphamide chemotherapy (Patient Characteristics, page 361), reactivating the patient's thymus by administering LHRH agonist leuprolide

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intravenously or orally in a pharmaceutical composition before, at the time, or after receiving donor cells (Leuprolide Administration, page 361), which would reactivate thymus through disruption of sex steroid-mediated signaling to the thymus; wherein the patients are post-pubertal (median age 26), wherein the patients had chemotherapy or radiation therapy (minor or full myeloablation), received autologous and allogeneic bone marrow transplantation respectively, which BM contains CD34+ HSCs, and hence the patient would have an increased tolerance to a graft compared to an untreated donor.

Ghalie et al use an LHRH analog, and hematopoietic stem cells (kit) for treatment.

Accordingly, *Ghalie et al* anticipate instant claims.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 19, 20, 23, 25, 28-31, 34-36, 38-40, 42, 43, 46-49, 55, 57-60, 62, 64-66, 68-70 are rejected under 35 U.S.C. 103(a) as being unpatentable over *Mardiney, III et al* (USP 6,863,885), in view of the BBC News (December 1998), and *Windmill et al* (Tissue Cell. 1998;30:104-11).

Mardiney, III et al teach a method for allogenic (mismatched donor) graft (inducing tolerance to a graft) comprising administering hematopoietic growth factors and cytokines, ablating the patient's T cells by non-myeloablative dose of radiation or

chemotherapy, followed by hematopoietic stem cell transplantation. *Mardiney, III et al* teach the radiation eradicates diseased blood cells, while the growth factor promotes the regeneration of new blood cells (e.g. column 3). *Mardiney, III et al* established the state of the art with respect to inducing tolerance to allogenic grafts, which is a pre-conditioning regimen that includes either high dose radiation/chemotherapy or a lower dose non-myeloablative regimen accompanied by hematopoietic growth factors and cytokines (e.g. claims). *Mardiney, III et al* go on to teach the goal of a pre-conditioning regimen is to eliminate diseased cells such as leukemia/lymphoma, to create an environment in the recipient in which the donor's HPCs can successfully engraft by homing into the recipient's bone marrow to further undergo hematopoiesis, and serve as an immunosuppressive agent to mitigate graft rejection in the treatment of non-cancerous diseases (e.g. column 1). *Mardiney III, et al* do not teach using thymus reactivation in the transplantation procedure.

The cited BBC News supplemented the deficiency by establishing it was known in the art that chemical castration via sex hormones can restore/regenerate thymus function and thus be used at the time of transplantation to promote the recovery of immunosuppressed recipient. Although the News did not give details about castration and thymus regeneration, the teaching of *Windmill et al* evidenced that it was known in the art before the instant priority date, castration could increase the weight of thymus, as well as the numbers and responsiveness of T cells in peripheral blood (e.g. abstract), and it was also known in the art sex hormones are closely interrelated with thymus function and immune system (Introduction and Discussion).

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the method taught by *Mardiney, III et al*, by combining the chemical or surgical castration in the transplantation protocol with a reasonable expectation of success. The ordinary skilled artisan would have been motivated to do so for added benefit of restoring the recipient hemotopoietic system or in complex clinical cases, where additional measurement to ensure the success of stem cell transplantation is required. Although the combined teachings do not specify a kit or the LHRH antagonists known in the art, it would have been obvious to the skilled in the art to assemble a kit containing active ingredients to be used in the combined therapy for the ease of commercial activity. Thus, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Q. Janice Li** whose telephone number is **571-272-0730**. The examiner can normally be reached on 9:30 am - 7 p.m., Monday through Friday, except every other Wednesday.

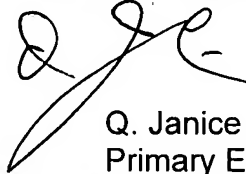
If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Joseph Woitach** can be reached on **571-272-0739**. The fax numbers for the organization where this application or proceeding is assigned are **571-273-8300**.

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Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

**Q. JANICE LI, M.D.
PRIMARY EXAMINER**

A handwritten signature in black ink, appearing to be 'Q. Janice Li', written over a horizontal line.

Q. Janice Li, M.D.
Primary Examiner
Art Unit 1633

QJL
October 24, 2007